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Cognitive impairment among prostate cancer patients: an overview of reviews

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Abstract

To identify and clarify definitions and methods of measuring cancer-related cognitive impairment among prostate cancer patients treated with Androgen Deprivation Therapy (ADT) and to assess the incidence and prevalence of cognitive impairment. A systematic review of Medline, EMBASE, PubMed, PsycINFO and CINAHL up to December 2015 was undertaken to identify English-language reviews. A total of twenty-eight reviews were identified describing twenty primary studies. There were no studies of incidence. Reported prevalence rates varied between 10 and 69%. Cognitive domains impaired by ADT included: verbal memory, visuospatial ability and executive functions. Cognitive impairment was infrequently defined and four definitions were reported. A variety of measures and methods were used to assess cognitive function including neuropsychological tests, self-report measures and clinical assessments. The finding that, often, one measure was used to assess more than one aspect of cognition is likely to have contributed to imprecise estimates. There is a need to agree a definition of cognitive impairment in the clinical epidemiology of cancer and to standardise the selection of measures in order to aid accurate assessment and fair comparisons across studies regarding the prevalence of cognitive impairment among prostate cancer patients.

Keywords: Prostate Cancer, Review, Psychological, Therapy

Introduction

Cognitive impairment among cancer patients may be due to psychosocial factors related to diagnosis or a shared aetiological pathway with tumour growth e.g. inflammatory response of the immune system (Lange et al. 2014; Myers 2009). Treatment-related factors among non-central nervous system (CNS) tumours beyond chemotherapy may also be implicated. Increasing research attention is being directed towards the side effects of androgen deprivation therapy (ADT) among prostate cancer patients beyond urinary and sexual dysfunction. Increasingly, cognitive impairment is being observed among prostate cancer patients as ADT restricts the production of androgens in order to inhibit tumour growth whilst potentially having a detrimental effect on cognition (Green et al. 2002). Cancer-related cognitive impairment has a significant impact on the ability of patients to make informed choices about their treatment (Nelson et al. 2007) and on activities of daily living and overall quality of life (Wu et al. 2013). There is a lack of clarity about the clinical epidemiology of cognitive impairment among prostate cancer patients. A brief scoping review was conducted in order to inform our intervention research and development work designed to reduce cognitive impairment in cancer patients (Treanor et al., in preparation) and a number of relevant published reviews were identified. This paper, therefore, identifies and synthesises studies regarding the incidence, prevalence, definition and measurement of cognitive impairment among prostate cancer patients by conducting a review of reviews.

Methods

Search

This review was guided by the Centre for Review and Dissemination's handbook for systematic reviews (Centre for Reviews and Dissemination 2009). A search of MEDLINE, EMBASE, PsycINFO, CINAHL and Social Sciences Citation Index was undertaken in December 2015.

The search was restricted to reviews published after 1980 as research directed towards cancer-related cognitive impairment began to appear in the literature at this time. We combined terms describing prostate cancer, cognitive impairment and reviews (see Figure i for full search strategy). Identified papers were exported to Refworks where duplicate papers were removed. Two authors (CT and JL) independently reviewed each title, abstract and full paper. Discussions were held to identify any discrepancies in studies for inclusion and a consensus was reached. A third author (MD) was available if a consensus could not be reached regarding paper inclusion.

Inclusion and exclusion criteria

Reviews which addressed at least one aspect of the epidemiology of cognitive impairment including incidence, prevalence, definition and measurement of cognitive impairment among prostate cancer patients were included as were reviews of studies of patients who had completed or were currently receiving ADT in isolation or in combination with other treatments. The scoping review indicated that many published reviews did not report their review methods so it was not possible to judge whether they were conducted systematically. So, papers which were described and/or indexed as a review were included. Reviews of prostate cancer patients in palliative care and studies that addressed cognitive impairment across multiple cancer sites unless separate data were available for prostate cancer patients were excluded.

A total of 143 papers remained for title screening after duplicates had been removed. Forty-seven papers remained following abstract screen and twenty-five full papers were reviewed for inclusion in the review. Sixteen reviews met the inclusion criteria and were included in the review. A further twelve studies were identified from the citation lists of included studies. In

total, twenty-eight papers are included in the review. Figure ii outlines the screening process. Data were independently extracted, then compared and discussed by the research team.

Results

Review characteristics

Twenty-eight reviews (Ahles & Saykin 2007; Artherholt & Fann 2012; Beauchet 2006; Biegler et al. 2009; Chen & Petrylak 2004; Chism & Kunkel 2009; Droz et al. 2010; Falci et al. 2009; Green et al. 2005; Grossmann & Zajac 2011; Gruca et al. 2012; Harrington et al. 2010; Holzbeierlein 2006; Isbarn et al. 2009; Jamadar et al. 2012; Janelins et al. 2011; Mitsiades et al. 2008; Mohile et al. 2009; Mottet et al. 2006; Nelson et al. 2008; Scherr & Pitts 2003; Sharifi 2005; Trost et al. 2013; Tombal 2009; Wefel et al. 2004; Wright et al. 2006; Ziolkowska et al. 2012) described twenty primary studies (Alibhai et al. 2010; Almeida et al. 2004; Beer et al. 2006; Beer et al. 2004; Bloomfield & Shilling 2004; Bussiere et al. 2005; Cherrier et al. 2003; Cherrier et al. 2009; DiBlasio et al. 2008; Green et al. 2002; Green et al. 2004; Jenkins et al. 2005; Joly et al. 2006; Mohile et al. 2010; Salminen et al. 2005; Salminen et al. 2004; Salminen et al. 2003; Shahinian et al. 2006; Verhagen et al. 2008)- see Table i for review characteristics. The reviews were conducted by institutions in USA (n=19), Europe (n=8) and Canada (n=1). Twenty-two reviews focussed on the uses and side-effects of ADT, one review focussed exclusively on ADT-related cognitive impairment; the remaining reviews focussed generally on cancer- or treatment-related cognitive impairment (n=7) and on general cancer-related side effects (n=4). Two reviews focussed on cancer within elderly populations with consideration given to treatment which may augment risk of cognitive impairment; other reviews considered testosterone (n=1) and diethylstilboestrol (n=1) in relation to cognitive function among individuals with cancer. The reviews reported infrequently the prevalence, definition or measurement of cancer-related cognitive impairment among prostate cancer patients, thus this

information was extracted from the cited primary studies. None of the reviews reported on the incidence of cancer-related cognitive impairment among prostate cancer patients.

Definition

None of the reviews defined cognitive impairment; however, one review calculated Reliable Change Index (RCI) data from the primary studies (Jamadar et al. 2012). Many of the primary studies did not define cognitive impairment in any way. Four operational definitions of cognitive impairment were reported across the studies. A RCI which takes into account practice effects of performance on neuropsychological test measures was used in three studies (Jenkins et al. 2005; Green et al. 2002; Cherrier et al. 2003). Two further studies defined impairment in terms of deviation of scores on neuropsychological tests from population or non-cancer control norms i.e. 1.5 standard deviations (Salminen et al. 2004) or in terms of 1-, 2- or 3- deterioration points corresponding to 1.5-, 2- or 3- standard deviations (Mohile et al. 2010). Diagnostic criteria were used to define cognitive impairment in two studies: one study used International Classification of Diseases version 9 (ICD-9) codes for cognitive disorders (Shahinian et al. 2006) and a further study utilised criteria from the Diagnostic Statistical Manual of Mental Disorders version IV (DSM-IV) (DiBlasio et al. 2008). A further study utilised categorical cut-offs on the established High Sensitivity Cognitive Screen (HSCS) measure to define levels of impairment including normal functioning, mild-, moderate- or severe- impairment (Joly et al. 2006).

Measurement

Aspects of cognition measured across the studies are reported in Table ii. Verbal fluency, verbal memory, visuospatial ability, visual memory, general executive functions and attention were frequently captured across the studies. Neuropsychological test measures were frequently used to capture cognitive function objectively, although, self-reported measures to capture

subjectively reported cognition and clinical diagnostic criteria were also used. For many of the cognitive domains a diverse range of neuropsychological test measures were utilised; in the instance of verbal memory fifteen separate measures or sub-tests were used. Measures infrequently capture overall cognitive function and one test measure was identified known as the Cambridge Examination for Mental Disorders of the Elderly-Cognitive Battery (CAMCO-G). A computerised neuropsychological test called CogniSpeed was used in three studies (Salminen et al. 2003; Salminen et al. 2004; Salminen et al. 2005). Some neuropsychological test measures were used to assess as many as three different cognitive domains, for example, the Weschler Adult Intelligence Scale (WAIS) digit symbol was used to assess visuospatial ability, spatial memory and attention (see Table iii).

Prevalence

Similar proportions of prostate cancer patients were found to have cognitive decline on neuropsychological test measures across four studies.

In one study, 52% of men over the age of 50 years who were due to initiate at least 6-months ADT for prostate cancer scored 1.5 standard deviations below population norms for verbal- and visual- memory. Moreover, 45% met the criteria for mild cognitive impairment at 6-month follow-up. The authors also calculated a RCI for each test measure. Declines were observed in executive functions among 38% of prostate cancer patients, visuospatial ability among 24%, verbal memory among 19%, verbal fluency among 14% and visual memory among 10% of patients (Mohile et al. 2010).

Additionally, approximately 50% of men with prostate cancer demonstrated reliable decline on 7 out of 8 neuropsychological tests before initiation of intermittent ADT (IADT) to 9-months of treatment. Declines on specific cognitive domains include spatial ability (69%) during ADT, whereas, 15% of men experienced decline 3-months off-ADT (Cherrier et al. 2003).

One study randomised 82 men with localised prostate cancer (mean age 73.3 years) to active surveillance or hormonal therapy. Neuropsychological assessments were taken at baseline one week prior to ADT initiation and 6-months later. Prevalence of cognitive impairment was operationalised in terms of a RCI. Forty-eight per cent (n=24) and 14% (n=7) of men on ADT demonstrated reliable decline since baseline on at least one or two neuropsychological test measures, respectively. Declines were commonly experienced in the attention and verbal memory domains. There was an absence of reliable decline among men who were being actively monitored (Green et al. 2002).

A similar proportion of men with prostate cancer (47%) demonstrated reliable decline on at least one neuropsychological test measure from baseline (pre-luteinizing hormone releasing hormone (LHRH) use) to 3-months of-, or, completion of-, LHRH. This impairment was experienced commonly in visuospatial ability and memory. Compared to men without prostate cancer, men who received LHRH had a significant fourfold increase in odds of cognitive decline on at least one measure (Odds ratio (OR) =4.412; p=0.03). At the nine-month assessment point reliable decline was observed among 34% (n=11) of men with prostate cancer compared to 28% (n=5) of men without prostate cancer (OR=1.37, p=0.63). Again, the impairment was predominantly related to visuospatial ability (Jenkins et al. 2005).

A cohort study utilising the Surveillance Epidemiology and End Results (SEER) programme identified 101,089 men, including men with prostate cancer who were undergoing ADT (n=15,748) or not undergoing ADT (n=34,685) and men without cancer (n=50,476). There was a significant difference (p<0.001) in the proportion of men with cognitive disorders (according to ICD-9 codes) across groups: 13.9% of prostate cancer patients receiving ADT, 10.2% of prostate cancer patients not receiving ADT and 7.9% of men without cancer. Results from unadjusted Cox proportional hazard models indicate that prostate cancer patients receiving ADT have a 44% increased risk of a cognitive disorder compared to prostate cancer patients

who have not underwent ADT (Risk Ratio (RR) =1.44, 95% CI= 1.38-1.50). When adjustment was made for a number of individual-, cancer- and treatment-related variables, the elevated risk among men receiving ADT was no longer observed and no longer statistically significant (RR=0.99, 95% CI=0.94-1.04). The authors stratified their analysis to men under the age of 80 without comorbidities who had early-stage prostate cancer; in the unadjusted analysis there was an 29% increased risk of cognitive disorders among men who received ADT compared to those who had not (RR=1.29, 95% CI=1.13-1.46). The increased risk was reduced and no longer statistically significant in the adjusted analysis (RR=1.10, 95% CI= 0.96-1.26) (Shahinian et al. 2006). A further study identified 13.9% of men with prostate cancer developed dementia following ADT use (DiBlasio et al. 2008).

Utilising the HSCS, men with non-metastatic prostate cancer receiving ADT were compared to age-matched men without cancer in terms of whether they scored as having normal/mild (n/m) cognitive impairment or moderate/severe (m/s) cognitive impairment. Seventy-seven percent and 23% of men with prostate cancer were scored as having n/m and m/s overall cognitive impairment, respectively. For the remaining cognitive domains the proportions are as follows: memory (n/m: 82%; m/s: 23%), attention (n/m: 96%; m/s: 4%), spatial ability (n/m: 86%; m-s: 14%), visuospatial ability (n/m: 100%; m/s: 0%), language (n/m: 82%; m/s: 18%) and planning (n/m: 95%; m/s: 5%). The differences between groups were not statistically significant (Joly et al. 2006).

Although many of the studies did not report the proportion of men who experienced cognitive impairment, patterns of impairment were observed in verbal memory (Green et al. 2004), attention (Green et al. 2002) and of being diagnosed with a clinically important cognitive disorder (Shahinian et al. 2006) among men who received ADT compared to men who did not receive ADT.

The premise of intermittent ADT is that many of the side effects of ADT can be attenuated during the non-treatment, 'wash-out' period. This was supported in two studies (Cherrier et al. 2003; Almeida et al. 2004), however, men receiving Intermittent ADT reported poorer scores on a self-reported cognitive function measure compared to men receiving continuous ADT (Verhagen et al. 2008).

Compared to men without cancer, poorer test performance was observed among men with prostate cancer receiving ADT in verbal memory (Green et al. 2004; Salminen et al. 2003; Beer et al. 2006), attention (Green et al. 2004; Salminen et al. 2003), visuospatial ability (Salminen et al. 2003; Cherrier et al. 2009), executive functions (general) (Cherrier et al. 2009), and processing speed (Beer et al. 2006).

Improvements in cognitive function among men with prostate cancer receiving ADT were reported in a small number of studies. Improvements in verbal memory (24%), visual memory (10%), visuospatial ability (48%), executive functions (29%) and language (10%) were observed in one study (Mohile et al. 2010). Using a RCI to determine improvement in cognitive function, 5-6% of prostate cancer patients receiving treatment improved on one or more test. With regards to individual cognitive domains, 4-9% of patients improved on verbal ability, 13% improved on visuospatial ability and 4-7% improved on working memory (Jenkins et al. 2005). Compared to baseline scores, an improvement among prostate cancer patients in episodic and semantic memory (Salminen et al. 2003) and object recall (Salminen et al. 2004) after 12-months of ADT was observed. When exposed to the same stimuli, improvements in memory were observed among prostate cancer patients on active ADT up to 12 months post-baseline assessment (Green et al. 2004). Verbal ability improved for a sub-group of prostate cancer patients receiving cyproterone (Green et al. 2002).

Discussion

There was considerable variation across studies in terms of the prevalence of cognitive impairment among men with prostate cancer who received ADT. Prevalence rates ranged from as low as 10% for RCI decline in visual memory to as high as 69% for RCI decline for spatial ability. Regarding specific cognitive domains such as visuospatial ability, again estimates varied widely from 24-69%. This variation may be explained by the type of treatment received by men in studies (e.g. Intermittent ADT versus continuous ADT) and length of time until follow-up assessment was conducted (e.g. 6 months versus 9 months). Moreover, none of the studies which reported a prevalence rate for visuospatial decline among prostate cancer patients used a common assessment measure making it difficult to make comparisons. This was true across all studies. There was less variability in cognitive impairment assessed according to clinical criteria. There was consistency in reported prevalence rates of cognitive impairment (13.9%) in two studies which utilised different clinical criteria (ICD-9 versus DSM-IV). As expected, cases of clinically assessed and defined cognitive disorders were lower than scores on neuropsychological tests. Cancer-related cognitive impairment is often described as mild or moderate so may not be of the level of severity required to meet clinically defined criteria. Therefore, it is likely that neuropsychological tests may be more sensitive to capture the subtle changes in cognitive function among cancer patients than clinical criteria. A potential explanation for the reported variation in prevalence rates is the use of diverse measures to assess cognitive domains as evidenced by, for example, 15 separate tests to assess verbal memory. Due to the number of measures used across studies it is difficult to discern any one measure that should be recommended to assess individual cognitive domains among prostate cancer patients.

There is a need to clarify and agree a definition of cognitive impairment in the clinical epidemiology of cancer and to standardise the selection of measures in order to aid accurate assessment and fair comparisons across studies regarding the prevalence and rate of cognitive

impairment among men with prostate cancer. The general pattern of impairment among prostate cancer patients treated with ADT tends to relate to executive functions, visuospatial-, verbal- memory, verbal fluency and spatial ability. Many of the studies were observational, whereas a few studies were of an experimental design and there was variability in the use of appropriate comparators. Many studies included healthy men without cancer as controls, however, the extent to which this kind of control is appropriate is questionable given that disease-related factors associated with cognitive function cannot be taken into account. Neuroimaging techniques may be used as an additional objective assessment to elucidate further the effects on ADT on cognitive functions (Chao et al. 2013).

The focus of this review was on cognitive impairment among men with prostate cancer treated with ADT. However, it is instructive to note that *improvements* in functions were observed and that some studies reported no differences between men with prostate cancer and men without cancer and men not treated with ADT. In the case of verbal memory and visuospatial ability in one study (Mohile et al. 2010) the number of men who improved was greater than the number of men who declined; as these changes in scores were calculated using a RCI the rate of improvement is beyond practice effects only. Further analysis by the study authors suggest that men with average or better than average scores at baseline demonstrated improvements over the course of the study. The remaining studies that reported improvements in cognitive function among prostate cancer patients were unable to discern individual risk factors for the increased risk of development of cognitive impairment.

As noted above, many papers did not clearly operationalise cognitive impairment and it is important that future studies provide clear definitions. In particular, the use of methods such as a RCI which take into account practice effects may provide an indication of clinically relevant cognitive impairment among prostate cancer patients. It may appear unusual that a larger number of reviews than primary studies were identified; this is in part due to the varying focus

of the included reviews, with many reviews not focused specifically on ADT-related cognitive impairment.

Strengths and limitations

An important component of a review of reviews is an appraisal of the methodological quality of each paper using tools such as the Assessment of Multiple Systematic Reviews (AMSTAR) (Shea et al. 2007). We did not assess methodological quality per se because the reviews did not address specifically our research questions and because along with the primary studies in the reviews, we used the reviews to find and extract data about conceptual aspects and the nature and prevalence of cognitive impairment. This paper presents a synthesis of the only available research on the epidemiology of cognitive impairment among prostate cancer patients.

Conclusion

The variation in use of measures and infrequently reported definitions of impairment has contributed to a wide variation in reported prevalence rates of impairment among prostate cancer patients receiving ADT. Consistent use of measures with a clear operationalised definition of impairment within well-designed and powered studies are needed in the future in order to calculate accurate estimates, identify at-risk patients and design and deliver appropriate and effective preventative and compensatory strategies that address cognitive decline in this already vulnerable group of patients.

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